Blood Products Advisory Committee
67th Meeting, September 15, 2000

Classification of HLA Devices

I. Introduction

FDA is seeking recommendations regarding the formal classification of HLA Devices. Today's presentations are directed at providing the Committee with 1) an overview of the current regulatory status of HLA devices, 2) background regarding medical device classification, and 3) an overview of the Third Party Review Program. This effort was prompted by 1) recent complaints from portions of the industry that FDA review and enforcement are inconsistent and inequitable, 2) recent requests for clarification of the regulatory status of HLA devices from field investigators, and 3) recent initiatives to include Center for Biologics Evaluation and Research (CBER) regulated devices in the Third Party Review Program under the Food and Drug Administration Modernization Act of 1997 (FDAMA).

II. Background

There are a variety of in vitro diagnostics (IVDs) that fall into the category that we are referring to today as HLA devices. They include characterized leukocytes for detection and identification of antibodies to HLA antigens, characterized polyclonal and monoclonal antibodies for determination of HLA phenotypes, and DNA-based assays for determination of HLA genotypes. These IVDs are used in testing to support platelet and leukocyte transfusion, organ and bone marrow transplantation, and paternity and forensic studies. We are not including those IVDs used to predict disease, e.g., HLA B-27 as a marker for ankylosing spondylitis, in this discussion. Those IVDs are regulated by the Center for Devices and Radiological Health (CDRH).

The first of these devices to be regulated were polyclonal antibodies for determination of HLA phenotypes. These products were called Leukocyte Typing Serum and were licensed under the Public Health Service Act (PHS Act). The first of three licenses was issued in December 1974. An FDA guideline for the production, testing and lot release of the product was issued in 1977 and subsequently codified as Additional Standards under the Biologics regulations. These included standards for potency, specificity, processing methods, labeling, and lot-by-lot release.

On August 1, 1980, FDA published a proposed rule recommending that the additional standards for Leukocyte Typing Serum be revoked with the subsequent revocation of the existing product licenses. The proposal was prompted by the realization of the growing complexities of the HLA system and the difficulty in achieving standardization. The proposal was supported by the argument that the products, while biologics, were also medical devices which could be appropriately and efficiently regulated under the Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act (act).

On August 10, 1982, after receiving only three comments, all of them supportive of the proposed rule, FDA published a final rule revoking the additional standards for Leukocyte Typing Serum. The final rule also announced the removal of Leukocyte Typing Serum from the dating period requirements under 21 CFR 610.53, revocation of establishment and product licenses for the

product, rescission of the 1977 FDA guideline, and elimination of the requirements for lot release. It went on to clarify that although the product would be regulated solely as a device, CBER (Office of Biologics at that time) would continue to be the lead in regulating the products. It instructed all manufacturers of Leukocyte Typing Serum to register and list under Part 807, and if not currently licensed, submit premarket notifications (510(k) submissions).

At the time of issuance of the final rule, the device had not yet been formally classified. The agency's intent to classify the device was spelled out in the preamble to the 1980 proposed rule. There was apparently speculation that the device might be classified as a Class I device as evidenced by the statement "If this proposal is published in final form, Leukocyte Typing Serum shall be subject to the general control provisions of the act..." On the other hand, the fact that the device had previously been subject to additional standards and special labeling requirements, i.e., special controls, would indicate that it might be more appropriate to classify the device as a Class II device. In the end, a final decision was not reached and a formal classification was never published.

III. Current Issues

Subsequent to the issuance of the final rule, CBER received, reviewed, and cleared a number of 510(k) submissions for additional devices, as described previously. Because of the lack of a formal classification and the uncertainty of the agency's intent, letters to manufacturers of HLA devices have variably referenced them as Class I or Class II devices. Recent requests for clarification of these discrepancies lead to a review of the history of the regulation of these devices, which is summarized above. Letters to HLA device manufacturers now state that the device is unclassified.

Lack of a formal classification has also caused confusion for new manufacturers of HLA devices. Upon attempting to determine the regulatory requirements for these devices, new manufacturers find that the device is not classified and mistakenly believe that they do not need to register and list and that no 510(k) submission is needed. The agency has anecdotal reports that there are products on the market without appropriate clearance.

Furthermore, since field enforcement resources are often assigned based on the classification of the device, there has been confusion about surveillance of HLA device manufacturers. Class I devices are generally accepted to be low-risk devices whereas Class II devices are accepted to be moderate-risk devices. Therefore, when there are resource constraints, enforcement is usually based on risk. As a result of the failure of manufacturers to register and list and the issuance of some letters stating that the devices are Class I, most HLA device manufacturers have not been inspected recently.

Lastly, to meet the requirements of FDAMA, CDRH is basing a number of their re-engineering initiatives on risk(s) associated with a device and its classification. Some of these risk-based initiatives include exemption of low-risk or moderate-risk (most Class I devices and approximately 66 Class II devices) from submission of 510(k)s, alternative methods for demonstrating substantial equivalence (the New 510(k) Paradigm), and the Third Party Review Program. CBER is actively pursuing the implementation of these new initiatives. HLA devices have been identified as being devices that are ideally suited for Third Party Review. However, it is important that a Third Party Reviewer understand what class a device belongs in.

IV. Device Classification

A. Classification of Preamendments Devices

The act requires FDA to obtain a panel recommendation and to issue proposed and final regulations classifying devices—such as HLA devices—that were on the market at the time of enactment of the Medical Device Amendments of 1976 ("preamendments devices"). There are three regulatory classes into which FDA places all preamendments devices. This classification is based on the level of control necessary to assure safety and effectiveness of the device. The three classes are Class I, Class II, and Class III.

A device is placed in Class I if general controls alone are sufficient to provide reasonable assurance of safety and effectiveness or if it is unclear that general controls alone are sufficient to provide reasonable assurance of safety and effectiveness but the device is not life-supporting, life-sustaining, or of substantial importance in preventing impairment of human health. This is the least stringent regulatory category for medical devices. General controls include establishment registration, product listing, conformance to the Quality System Regulation (formerly the Good Manufacturing Practices regulation), conformance to device labeling requirements, submission of a Premarket Notification (510(k) submission), and various other provisions of the act. However, it should be noted that as a result of FDAMA, most Class I devices are now exempt from the requirement to submit a 510(k). Also, most Class I devices are not subject to the design controls provisions of the QSR, and some Class I devices are exempt from other QSR requirements. An example of a Class I device used in establishments that manufacture blood and blood products is a blood grouping view box.

A device is placed in Class II if general controls alone are insufficient to provide reasonable assurance of safety and effectiveness and there is sufficient information to establish special controls. These devices are generally moderate-risk devices but may be life-supporting or life-sustaining. Special controls include performance standards, special labeling requirements, guidance documents, recommendations, patient registries, post market surveillance, and "other actions deemed appropriate by the Commissioner." Special controls are applied in addition to general controls, not instead of, so the general controls described above also apply. An example of a Class II device used in establishments that manufacture blood and blood products is an automated blood grouping and antibody test system.

A device is placed in Class III if there is insufficient information to determine that general controls or application of special controls would provide assurance of safety and effectiveness and the device is life-supporting, life-sustaining, of substantial importance in preventing impairment of human health, or presents a potential, unreasonable risk of illness or injury. In addition to the application of general and special controls, premarket approval is required for these devices. FDA must issue a regulation calling for the submission of PMAs for a preamendments device that is classified in Class III. A Premarket Approval application (PMA) is submitted by the manufacturer to FDA for scientific and regulatory review to ensure the safety and effectiveness of the device. This is the most stringent regulatory category for medical devices. An example of a preamendments Class III device used in establishments that manufacture blood and blood products is an electromagnetic blood and plasma warming device.

B. Classification of Postamendments Devices

A device that is introduced to the market after enactment of the Medical Device Amendments of 1976 ("postamendments device") is in the same regulatory class and is subject to the same requirements as a preamendments device (or reclassified postamendments device) to which it is determined by FDA to be "substantially equivalent." (The term "substantially equivalent" is defined in section 513(i) of the act.) FDA determines whether a new device is "substantially equivalent" by reviewing a Premarket Notification (510(k)) submission from the manufacturer. A device that is not determined to be "substantially equivalent" is automatically in Class III and is immediately subject to premarket approval requirements, unless it is reclassified by FDA. Examples of "not substantially equivalent" Class III devices include HIV test kits for diagnosis, prognosis, or treatment, and home collection kits for HIV testing.

V. Other Considerations

Once the appropriate classification of HLA devices is determined, other decisions regarding how they should be regulated can be made. For example, Class I devices need to be assessed to determine if they should be exempt from 510(k) requirements or if they should be reserved (not exempt). If a device is assigned to Class II, special controls need to be identified. For HLA devices, there are currently special labeling controls in place. If these devices are placed in Class II, it is FDA's intention to expand these special controls by developing a guidance document for reviewers and industry. A Class II device may also be exempted from 510(k) requirements if 510(k) submissions are not necessary to assure the safety and effectiveness of the device. Once those decisions are made, it can be determined if Third Party Review is appropriate.

VI. Question to the Committee

Does the Committee agree that HLA devices (for use in detecting antibodies to HLA antigens or determining HLA phenotype or genotype) should be classified as Class II devices?

The following information is needed from the Committee.

- A recommendation respecting the classification of HLA devices, including:
  - a summary of the reasons for the recommendation;
  - a summary of the data upon which the recommendation is based; and
  - an identification of the risks to health (if any) presented by the devices.
- If the Committee recommends Class I: A recommendation as to whether HLA devices should be exempted from the requirements of section 510(k) (Premarket Notification), 519 (Records and Reports), or 520(f) (Good Manufacturing Practice Requirements).
- If the Committee recommends Class II: Identification of special controls for HLA devices, and a recommendation as to whether HLA devices should be exempted from 510(k) requirements.
- If the Committee recommends Class III: A recommendation for the assignment of a priority for the application of Premarket Approval requirements to HLA devices.